REMARKS/ARGUMENTS

Claims 31-34 are pending in the above-identified application. In view of the remarks set forth herein, reconsideration of all pending claims is respectfully requested.

Double Patenting

The Examiner has maintained the rejections of claims 31-34 under the judicially created doctrine of obviousness-type double patenting as follows:

Claims 31, 33, and 34 as allegedly unpatentable over claims 1, 3, 5, and 9 of U.S. Patent No. 5,885,971;

Claims 31-34 as allegedly unpatentable over claim 6 of U.S. patent No. 6,004,944;

Claims 31, 33, and 34 as allegedly unpatentable over claims 1, 2, 4, 7 and 8 of U.S. Patent No. 6,255,289; and

Claims 31-34 as allegedly unpatentable over claim 1 of U.S. patent No. 6,531,455.

As previously indicated, Applicants agree to submit an appropriate terminal disclaimer upon an indication of otherwise allowable subject matter. The filing of a terminal disclaimer should not be construed as acquiescence in the rejection.

Rejections under 35 U.S.C. § 103

Claims 31-33

The Examiner has maintained the rejections of claims 31-33 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Hickman *et al.* in view of Yang *et al.* The Examiner contends that the cited art "clearly teaches that hepatic intraductal administration of naked DNA is an efficient way to delivery proteins to the bloodstream," and that one of skill in the art, reading Hickman and Yang, "would have been motivated to use intraductal delivery of

naked DNA in place of Hickman's approach of direct injection into the liver." (Office Action at pp. 4 & 5.)

Applicants maintain traversal of the instant rejection. For the reasons set forth herein, a case of obviousness of the present claims over Hickman and Yang has not been established. To show non-obviousness of the present claims, Applicants submit herewith the Declaration of Michael S. German under 37 C.F.R. § 1.132 (hereinafter the "German Declaration"). The German Declaration addresses the Examiner's remarks in the Office Action and shows that Hickman and Yang do not teach that hepatic intraductal administration of naked DNA is an efficient way to deliver proteins to the bloodstream, and further that, as of the filing date of the '893 application, the skilled artisan reading Hickman and Yang would not have led to modify Hickman in the manner proposed by the Examiner. (*See* German Declaration at ¶ 7.)

First, Applicants again note that a *prima facie* case under 35 U.S.C. § 103 requires a clear and particular showing, in the prior art, of a motivation sufficient to impel one to do specifically what applicant has done. To establish the *prima facie* case, the Examiner must show, *inter alia*, some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a reference or combine reference teachings so as to achieve the specific combination as claimed by the applicant. *See* MPEP at §§ 2142 and 2143.01; *In re Fine*, 5 USPQ2d at 1598, 1599 (Fed. Cir. 1988); *In re Dance*, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). The suggestion or motivation to make the claimed combination must be found in the prior art and cannot be based on applicant's disclosure. MPEP § 2142; *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). *See also* MPEP §§ 2143 and 2143.01 (citing cases). The cited art must be considered in its entirety, including portions that would teach away from the claimed invention. *Id.* at § 2141.02 (VI) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.* 220 USPQ 303 (Fed. Cir. 1983)). Moreover, the proposed motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (Bd. Pat. App. Inter. 1993). The motivation must also be both objective and specific, *i.e.*, the Examiner's showing must be clear and particular. *See In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir.

1999). It is this requirement for evidence of particularized motivation that provides a safeguard against the "tempting but forbidden zone of hindsight." *Id.* at 1616.

In the present case, for the reasons set forth below, there is no clear and particular motivation in Hickman or Yang to substitute intraductal delivery of naked DNA in Hickman's method. (German Declaration at ¶ 23.) Accordingly, in view of the above standards, a case of obviousness of the present claims over Hickman and Yang has not been established.

First, for at least the reason that Yang discusses a method designed for selective targeting of biliary epithelial cells over hepatocytes, an ordinarily skilled artisan, reading Yang, would not have been specifically and objectively led to use Yang's teachings to modify the method of Hickman, which, in contrast to Yang, is focused on targeting of hepatocytes. (German Declaration at ¶ 11.) As discussed in Applicants' previous response, Hickman and Yang discuss two different approaches for liver-directed gene expression, each approach specifically targeting different cell types. Hickman discusses a method for gene delivery targeting hepatocytes by direct injection into the liver of plasmid DNA encoding luciferase, β-galactosidase, or α-1-antitrypsin. (German Declaration at ¶ 9, (citing Hickman at p. 1477 (Abstract & Overview Summary) and pp. 1480-1482 (Discussion)).) In contrast, Yang, which is focused on treatment of cystic fibrosis (CF), discusses the specific, targeted delivery of recombinant adenoviruses to epithelial cells of the biliary tract. (German Declaration at ¶ 10 (citing Yang at p. 4601 (Abstract) and p. 4602, second col., first full paragraph).) Yang points to the biliary epithelial cells as the primary target for treatment of CF via gene transfer, and specifically teaches away from other strategies that focus "exclusively on the hepatocyte as a target cell." (*Id.* (citing Yang at p. 4602, second col., first full paragraph).) As stated by Yang, the advantage of this approach "is the specificity of gene transfer achieved by virtue of the anatomical constraints of the compartment into which the virus is delivered; the ***primary target*** of gene transfer is the ***biliary epithelial cells***, with recombinant gene expression detected in a ***minority of hepatocytes***." (German Declaration at ¶ 10 (citing Yang at p. 4604).)

As to the Examiner's statements regarding Yang's transfection of some hepatocytes via intraductal delivery of adenoviral constructs, these statements do not reflect the

totality of Yang's teachings with regard to transfection of hepatocytes. (German Declaration at ¶ 13.) Although Yang shows that some hepatocytes were transfected with recombinant adenovirus, Yang further teaches that the transfection of hepatocytes via the intraductal route is very inefficient, even with the use of adenovirus, a vector normally regarded in the art as providing efficient gene transfer. Yang shows that only the *maximal* dose of virus used (2×10^{12} plaque-forming units (pfu)/ml) achieved any significant gene expression in hepatocytes. (Id. (citing Yang at p. 4603, first col., first full para., stating that the maximal concentration of virus "demonstrated *lacZ* expression in all of the biliary epithelial cells as well as >80% of the hepatocytes").) Using the next highest dose (1×10^{11} pfu/ml), recombinant gene transfer was observed in only "<1% of all hepatocytes while *lacZ* expression was retained in all intrahepatic bile duct epithelial cells." (German Declaration at ¶ 13, citing Yang.) This rapid diminishment of gene transfer to hepatocytes, with delivery of submaximal doses of adenoviral vector to the biliary tract, does not reasonably support a conclusion of efficient gene expression into hepatocytes using intraductal delivery. (German Declaration at ¶ 13.)

In view of Yang's teachings as discussed above, a skilled artisan reading Yang would not reasonably regard intraductal delivery of a recombinant vector as a particularly suitable means for achieving efficient transfection of hepatocytes. (German Declaration at ¶ 14.) For this reason as well as the reasons previously discussed, the skilled artisan reading Yang and Hickman would not be reasonably be led to substitute Yang's intraductal delivery method for Hickman's method of direct injection into the liver. (*Id.*)

Further, even assuming, *arguendo*, that the skilled artisan were to modify Hickman by substituting Yang's intraductal delivery, per Yang's disclosure, the skilled artisan would use intraductal delivery of recombinant adenovirus rather than naked DNA. (German Declaration at ¶ 15.) Yang's studies pertain only to recombinant gene transfer using recombinant adenovirus. Yang does not discuss the use of naked DNA for transfection of the ductal biliary epithelial cells. Because gene transfer using adenovirus is generally regarded in the art as more efficient than gene transfer with naked DNA, even a teaching of efficient gene transfer to hepatocytes with adenovirus, via an intraductal route, would not reasonably suggest to the skilled artisan that a similar level of gene transfer could be achieved with intraductally delivered naked

DNA. (*Id.*) Indeed, in view of Yang's relatively poor gene expression in hepatocytes observed with intraductally delivered adenovirus, and because introduction of adenoviral vectors is generally known to be a more efficient means for achieving gene transfer than transfection with naked DNA, the skilled artisan would reasonably view Yang as teaching away from the use of naked DNA for achieving gene expression in hepatocytes by intraductal delivery. (*Id.* at ¶ 16.) Thus, there is no teaching or suggestion in Yang that delivery of a gene to hepatocytes can be achieved using intraductal delivery of naked DNA to the biliary epithelial cells. (*Id.* at ¶ 17.)

Accordingly, in light of Yang's disclosure and the knowledge in the art as summarized above, the skilled artisan reading Yang and Hickman would not be reasonably led to modify Hickman's method of gene transfer to hepatocytes by substituting intraductal delivery of naked DNA for Hickman's direct injection of vector into the liver. (German Declaration at ¶ 18.)

Moreover, the skilled artisan would not be reasonably led to modify Hickman with intraductal delivery because Hickman itself teaches away from administration routes other than direct injection into the liver. (German Declaration at ¶ 19.) Only hepatocytes near the site of injection expressed transgene. Hickman observed that, upon injection into the liver of media with DNA, the media with DNA visibly perfused a wider area of tissue than the limited zone exhibiting expression of the transgene (as shown by X-Gal staining). (*Id.* (citing Hickman at p. 1480, 1st col., last para. bridging to 2nd col.; and Figure 3).) Hickman concludes from this observation that "hepatocytes were transfected by a physical mechanism related to the actual injection procedure." (German Declaration at ¶ 19 (citing Hickman at p. 1480, 2nd col., top (emphasis provided).)

In view of this disclosure, the skilled artisan reading Hickman would not look to Yang's procedure of intraductal delivery as an advantageous or even suitable substitute for Hickman's direct injection. (German Declaration at ¶ 20.) Because only hepatocytes near the site of injection were transfected with plasmid, the skilled artisan would not reasonably expect intraductal delivery of naked DNA to hepatic duct epithileum to result in transfection of hepatocytes, located outside of the hepatic duct within the liver parenchyma. While Yang shows some gene transfer to hepatocytes, these results were achieved using recombinant adenovirus at

maximal doses, and not with naked DNA. Furthermore, because Hickman attributes gene transfer to hepatocytes to a "physical mechanism" related to the injection procedure, and because Yang's intraductal delivery to biliary epithelial cells would not be reasonably viewed by the skilled artisan as involving physical contact with hepatocytes in the same manner as Hickman's injection, a skilled artisan reading Hickman and Yang would not reasonably expect intraductal delivery of naked DNA to the biliary epithelial cells to achieve gene transfer to hepatocytes. (*Id.*)

With regard to the Examiner's assertion that Yang *et al.* "clearly teach the advantage of intraductal delivery for gene therapy," irrespective of any perceived advantage of a "nonsurgical approach," the skilled artisan would not view Hickman as particularly amenable to modification according to Yang's approach, for reasons already discussed above. (German Declaration at ¶ 22.) At the very least, any perceived advantage relating to a non-surgical aspect of intraductal delivery would be considered by the skilled artisan as outweighed by disadvantages as taught by Yang and Hickman, including (a) Yang's teaching of inefficient adenoviral gene transfer to hepatocytes, relative to the biliary epithelial cells, coupled with the knowledge in the art that naked DNA is generally less efficient than adenovirus for achieving gene transfer; and (b) Hickman's teaching that hepatocytes were transfected by a physical mechanism related to the actual injection procedure, suggesting that administration modes other than direct injection would not necessarily achieve gene transfer to hepatocytes. (*Id.*)

For at least all of the reasons above, a clear and particular motivation in the cited art to modify Hickman as proposed by the Examiner has not been established. Accordingly, the present claims are patentable over Hickman and Yang. Withdrawal of the rejection is respectfully requested.

Claim 34

Claim 34 remains rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Hickman taken with Yang, as applied to claims 31-33, and further in view of Heartlein *et al.* Applicants again traverse this rejection. As noted in Applicants' previous response, Heartlein

discusses *in vivo* delivery of human growth hormone (hGH) by transplantation of genetically engineered primary fibroblasts expressing the hGH gene. (*See* Heartlein at, *e.g.*, p. 10967, second col., first full paragraph.) Heartlein, however, does not discuss intraductal delivery of DNA into a secretory gland and therefore does nothing to cure the deficiencies of Hickman and Yang as set forth in the German Declaration. Accordingly, for reasons discussed with respect to the rejection of claims 31-33 in view of Hickman and Yang, a *prima facie* case of obviousness has not been established with respect to claim 34. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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